REMARKS

Entry of the foregoing amendments to the specification (including the title) and claims and substantive examination based on claims 54-113, as amended herein, is respectfully requested. Applicants submit that the foregoing amendments do not include any new matter.

EXPLANATION OF AMENDMENTS TO THE SPECIFICATION

1. The title is amended to identify the object of the process.

2. The three one sentence paragraphs beginning on page 24, line 22, and ending on page 25, line 2, are amended to add a reference to the SEQ ID NOS.1-8, respectively, for each of Figures 10-17. The substitute Drawings sheets for Figures 10-17 are amended accordingly.

3. The paragraph beginning on page 32, line 18 (under "Example 1"), and ending on page 33, line 3, is amended to insert the SEQ ID NO. 9 below the sequence shown on page 33, line 3.

4. The paragraph on page 33, lines 4-21, was amended to insert SEQ ID NO. 10 above the sequence shown on page 33, line 12, and SEQ ID NO. 11 above the sequence shown on page 33, line 21. In addition, the respective "*Hind*III" and "*Not*I" and "*Bam*HI" notation was moved closer to line showing SEQ ID NOS. 10 and 11.

5. The paragraph beginning on page 33, line 24 and ending on page 34, line 10, is amended to insert SEQ ID NO. 12 above the sequence shown on page 34 , line 6, and to insert SEQ ID NO. 13 above the sequence shown on page 33, line 10. In addition, the "*Hind*III" notation was moved closer to line showing SEQ ID NO.12.

6. The paragraph on page 35, lines 1-18, is amended to insert SEQ ID NO:14 above the sequence shown on page 35, line15. SEQ ID NO:15 has been inserted below the sequence shown on page 35, line 16. SEQ ID NO: 16 has been inserted below the sequence shown on page 35, line 18.

EXPLANATION OF AMENDMENTS TO THE CLAIMS

The amendments to the claims address the issues raised by the Examiner under "Claim Objections" and "Claim Rejections - 35 USC § 112" in the subject Office action.

1. Claims 54, 74 and 102 are currently amended to insert a period at the end of each in accordance with the examiner's comment.

2. Independent Claim 54 is further amended to include that the initial albumin solution in step (1) is "at pH 5.0 - 6.0". Basis for this limitation is found in the specification on page 6, lines 15-17, from which it is clear that pH 6.0 is the upper limit of the range, whereas, it is preferable to use a pH of at least 5.0.

3. Dependent Claims 55 and 57-60 are currently amended to replace the term "the initial albumin solution" with the term "the albumin solution subjected to cation exchange chromatography in step (1) of claim 54".

4. Dependent Claim 61 is currently amended to delete "pH adjustment" due to the PH range now included in step (1) of the main claim 54.

5. Independent Claim 76 is currently amended to include that the initial albumin solution in step(1) is "at pH 5.0 - 6.0".

6. Dependent Claim 77 is currently amended to replace the term "the initial albumin solution" with the term "the albumin solution subjected to cation exchange chromatography in step (1) of claim 76".

7. Independent Claim 79 is currently amended to include that the albumin solution in step(2) is "at pH 5.0 - 6.0".

8. Claim 80 is currently amended to replace the term "the initial albumin solution" with the term "the albumin solution subjected to anion exchange chromatography in step (1) of claim 79".

9. In order to overcome the examiner's objections in paragraphs 10 D, E, F and independent Claims 82, 83, 85, 87 and 90 are currently amended to add a semicolon and the phrase "thereby providing a purified albumin solution" at the end of each. (Rejected claims 84-86 and 91 each depends from one of these claims.)

10. Independent claims 82 and 83 are currently amended further to include that the albumin solution in negative mode cation exchange of step(ix) is "at pH 5.0 - 6.0".

11. Independent claims 86 and 87 are currently amended further include that the albumin solution in negative mode cation exchange of step(xi) is "at pH 5.0 - 6.0".

12. Independent Claim 90 is currently amended to include that the albumin solution in step(2) is "at pH 5.0 - 6.0".

13. Claim 91 is currently amended to replace the term "the initial albumin solution" with the term "the albumin solution subjected to anion exchange chromatography in step (1) of claim 90".

14. Independent Claim 111 is currently amended to include that the albumin solution in step(2) is "at pH 5.0 - 6.0".

15. Claim 112 is currently amended to replace the term "the initial albumin solution" with the term "the albumin solution subjected to anion exchange chromatography in step (1) of claim 111".

DRAWINGS

Substitute drawings are submitted herewith for Figures 9 and 10-17. Acceptance of the substitute drawings is respectfully solicited.

SEQUENCE COMPLIANCE REQUIREMENT

1. As noted above reference to SEQ ID NOS. has been added at the places in the specification identified by the Examiner. Thus, applicants submit that all sequences are properly identified.

2. A SEQUENCE LISTING is included herewith. A computer readable copy and the statement regarding its content with respect to the written form and that it contains no new matter are included (as well as a copy of the Notice to Comply).
Accordingly confirmation of applicants' compliance with the Sequence Requirements is respectfully solicited.

CLAIM OBJECTIONS

In view of the amendments to claims 54, 74 and 102 adding a period at the end of the claim presented herein, applicants respectfully request withdrawal of the objection.

CLAIM REJECTIONS - 35 USC § 112

Claims 55, 57-60, 77, 80, 82-89, 91 and 112 stand rejected under 35 USC 112, paragraph two. In view of the amendments to said claims presented herein and described in the EXPLANATION OF AMENDMENTS Nos. 3, 6, 8, 9, 13 and 15 above, applicants respectfully request withdrawal of the examiner's rejections in paragraph 10(A)-(I) of the subject Office Action.

CLAIM INTERPRETATION

Applicants note that the examiner's interpretation in paragraph 11 of the Office Action of "Chromatography in the negative mode with respect to albumin" is reversed. However, the correct interpretation - i.e., that "chromatography in the negative mode with respect to albumin" means that the albumin is not absorbed to the chromatographic matrix - has been applied in the body of the rejections under 35 USC 103(a) for obviousness.

CLAIM REJECTIONS - 35 USC § 103

In paragraphs 14-19 of the subject Office Action all of the claims, i.e., pending claims 54-113, are rejected for various reasons under 35 USC 103(a) as being obvious. Applicants respectfully request reconsideration and withdrawal of said rejections for the reasons given below.

In paragraph 14 of the subject Office Action, the examiner rejects claims 54, 56, 57, 59-67, 69, 70, 71, 74-76, 78, 79, 81, 90, 92, 93, 95-102, 104-106, 109-111 and 113 under 35 USC 103(a) as being unpatentable over Goodey et al. (WO97/31947; cited in the IDS) in view of Fisher et al. (US 4,228,154; cited in IDS), supported by Ohmura et al. (EP 0 570 916; cited in the IDS) and Lindquist et al. (US 4,086,222; cited in the IDS).

Applicants respectfully request reconsideration and withdrawal of this rejection for the reasons presented below.

In paragraph 14(B), the examiner states: "Goodey et al. **do not teach** albumin purification using CE or AE run in a negative mode" (emphasis added)

In paragraph 14(C) the examiner states: "Fisher et al. teach albumin purification using CE and AE chromatography in negative mode with respect to albumin (Abstract; co. 2, lines 12-16)."

Applicants note that Goodey et al has, as its main aim, highly pure albumin. This aim is stated on page 5, lines 16-28 of Goodey et al., and in particular lines 25-28, which states that –

"At least 99%, preferably at least 99.9%, by weight of the protein in the albumin preparations purified by the process of the invention is albumin".

Clearly Goodey tolerates a small amount of detectable non-albumin protein, specifically up to 1% non-albumin protein, in the albumin preparation produced although no more than 0.1% is preferred. However, the methods of the present application provide for

extremely pure albumin preparations. The examiner is referred to page 21, lines 5-11 of the present application, which states:

"The albumin is also characterized by extremely low levels of, or by being essentially free of, aluminum, lactate, citrate, metals, non-albumin human proteins, such as immunoglobulins, pre-kallikrein activator, transferrin, α_1-acid glycoprotein, haemoglobin and blood clotting factors, prokaryotic proteins, fragments of albumin, albumin aggregates or polymers, or endotoxin, bilirubin, haem, yeast proteins, animal proteins, and viruses. By essentially free is meant below detectable levels".

Thus it is quite clear that the present invention, which utilizes negative mode CE, provides methods wherein non-albumin proteins cannot be detected in the final preparation., i.e., providing an albumin product even more pure than that provided by Goodey et al.

By contrast, Fisher et al. (US 4,228,154) provides a method in which substantially lower levels of albumin purity are obtained. The examiner is referred to Table 1 therein, which bridges columns 5 and 6 of Fisher et al. The column of Table 1 entitled "*Electrophoresis % albumin*" shows that the method of Fisher et al. provides albumin having a level of purity between 96.9 and 98.9%. In other words, at best Fisher et al.'s product contains at least 1.1% non-albumin protein and the level of non-albumin protein contaminant can be more than 3%.

Goodey et al. teaches that the success of its method is reliant on the use of cation exchange chromatography in the positive mode with respect to albumin ("positive CE"), i.e. it binds albumin to the cation exchanger matrix whilst contaminants are washed away (see page 17, lines 2-6 and page 21, lines 16-20). In fact, Goodey et al. teaches that the best way to minimize non-albumin protein contamination is to use positive CE with a high salt buffer wash (see page 34, lines 9-23).

Given the emphasis placed in Goodey et al. on using positive CE to minimize non-albumin protein contamination, and the clear indication in Fisher et al. that a method utilizing negative CE results in greater contamination than is obtain by Goodey et al.'s positive CE method, it would not have been at all obvious to the skilled person to modify

the method of Goodey et al., to arrive at a method that utilizes negative CE such as claimed in the present application.

Therefore, having read Goodey et al., the skilled person would not be motivated to implement the teaching of Fisher et al., since he would expect that the albumin obtained would be less pure, i.e. contain more contaminants. In light of the teachings of Goodey et al. and Fisher et al. the skilled person would continue to use the method set forth in Goodey et al. without deviation.

Applicants submit further that the concept of "modifying" a positive mode chromatography to become a negative one is simply not permissible. The two forms of chromatography are mutually exclusive. The passage at page 31, lines 21-25 of Goodey et al. highlights the difference between the teaching of Goodey et al. of a positive mode CE and the negative mode CE of the present invention. The teaching in Goodey et al. here of using octanoate refers to conditions suitable for the elution of albumin from a positive mode cation exchange matrix. In other words, in Goodey et al. albumin is bound to the matrix and them eluted using octanoate at around pH 4.5, preferably about pH 5.5. By contrast, in the present invention, cation exchange is performed in the negative mode with respect to albumin, so albumin never binds to the cation exchange matrix. The use of octanoate at a pH of between 5.0 - 6.0 in the present invention ensures that albumin passes through the cation exchanger, while impurities are bound to the cation exchanger matrix.

Thus, in the negative mode CE, the elution step is not needed and the albumin product/solution passing to the next purification/treatment step has a different composition than that eluted from the positive mode CE matrix.

Applicants submit therefore that the examiner's recitation in paragraph 14(A)(2) that Goodey et al. teaches subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) Chromatography is inapposite.

Another basis for withdrawal of the rejection of the subject claims for obviousness over Goodey et al. in view of Fisher et al. concerns the amendment to independent claims 54, 76, 79, 90, and 111 which adds that the cation exchange chromatography (CE)

takes place at "pH 5.0 – 6.0". In this regard, Goodey et al. states instead a preferred pH of 4.0 – 5.0 at page 3, lines 18-21.

Furthermore, Fisher et al. teaches that cation exchange (CE) - in the negative mode - should be conducted at pH 4.5 - 4.9 (see column 2, lines 25-27). [Fisher et al. suggests a pH of 5.1 – 5.5 only in respect of an anionic exchange (see column 2, lines 30-32)] Therefore, even if Goodey et al. and Fisher et al. were combined (which applicants submit is an impermissible combination) then there is nothing in either of Goodey et al. or Fisher et al. to suggest to the skilled reader that cation exchange should be performed within the range pH 5.0 – 6.0.

Applicants therefore respectfully request withdrawal of the rejection of independent claims 54, 76, 79, 90, and 111 as being obvious over Goodey et al. in view of Fisher et al. Withdrawal of this rejection against dependent claims 55, 57-60, 69, 70, 74 and 75 which depend from claim 54; dependent claim 78 which depends from claim 76; dependent claim 81 which depends from claim 79; dependent claims 92, 93, 95-102, 104-106, 109, and110 which depend from claim 90; and dependent claim 113 which depends from claim 111 is also respectfully requested.

In paragraph 15 of the subject Office Action, the examiner rejects claims 55, 77, 80, 82 , 83, 84, 86, 88, 91 and 113 under 35 USC 103(a) as being unpatentable over Goodey et al. (WO97/31947; cited in the IDS) in view of Fisher et al. (US 4,228,154; cited in IDS), and further in view of Shaklai et al. (J.Biol.Chem., vol.259, pp 3812-3817, 1984).

Applicants respectfully request reconsideration and withdrawal of this rejection for the reasons presented below.

In paragraph 15(B), the examiner states: "Neither Goodey et al. nor Fisher et al. teach initial albumin solution containing glycosylated albumin and the glycosylated albumin being bound during the cation exchange step."

In order for obviousness to be determined from a combination of references, the references themselves must suggest the combination. In this case, the two primary references do not mention glycosylated albumin. Therefore, the references themselves

cannot suggest the combination asserted by the examiner to be obvious. Moreover, Fisher et al. and Shaklai et al. were available long before (1980 and 1984, respectively) Goodey et al. (1996 priority date) and Goodey et al. did not even mention this problem, let alone the use of applicant's negative mode CE. This is the epitome of unobviousness.

For these reasons applicants respectfully request withdrawal of the rejection of claims 55, 77, 80, 82 , 83, 84, 86, 88, 91 and 113 under 35 USC 103(a) as being unpatentable over Goodey et al. in view of Fisher et al. and further in view of Shaklai et al.

In paragraph 15(H) of the subject Office Action, the examiner specifically rejects independent claims 82 and 86 under 35 USC 103(a) as being unpatentable over Goodey et al. in view of Fisher et al. and Shaklai et al.

Applicants respectfully request reconsideration and withdrawal of the subject rejection for the reasons presented below.

Applicants submit that the combination of three references selected by the examiner to arrive at applicants' particular 13 step processes of claims 82 and 86 is not suggested in the references themselves. Accordingly, this combination is selected only in hindsight view of applicants' claims.

Goodey et al. discloses two specific 7 step processes as the second and third aspects of the invention disclosed therein. These are:

Goodey et al. page 2	Goodey et al. page 3 (& 38)
1) positive mode CE	1) positive mode CE
2) elution	2) elution
3) positive affinity chromatography	3) positive AE
4) elution	4) elution
5) gel permeation	5) positive affinity chromatography
6) positive AE	6) elution
7) elution	7) gel permeation
8) optional immobilized borate chrome	8) optional immobilized borate chrome

Goodey et al. does not mention the possibility of further purification steps and states on page 38 that that the purification process disclosed on page 3 (according to respective examples) is preferred. As seen above, both of these Goodey et al. processes include a gel permeation step.

Fisher et al., on the other hand , discloses only three purification steps, namely, (1) contacting the cryosupernatant plasma or its equivalent with a finely divided lipoprotein abstract, (2) negative mode CE, and (3) negative mode AE. As pointed out by the examiner, Fisher et al.'s reason for using both CE and AE in the negative mode is to retain the albumin in solution throughout the process.

Further, at the beginning of example 2, Fisher et al. states that the Cohn II + III supernatant albumin-containing material may be treated to remove alcohol and salt by gel filtration before step (1) above. Thus, it appears that Fisher et al. contemplates a gel permeation step as in both Goodey et al. 7 step processes. Applicants' processes of claims 83 and 87 do not include a gel permeation step.

As pointed out by the examiner, neither Goodey et al. nor Fisher et al. teach repeating AE chromatography steps. Additionally, as pointed out by applicants above, neither Goodey et al. nor Fisher et al. disclose running negative mode CE at a pH of 5.0 - 6.0. Goodey et al. states instead a preferred pH of 4.0 – 5.0 for CE at page 3, lines 18-21, and Fisher et al. teaches that cation exchange (CE) - in the negative mode - should be conducted at pH 4.5 - 4.9 (see column 2, lines 25-27). Thus, both Goodey et al. and Fisher et al. teach away from this condition for applicants' negative mode cation exchange chromatography step.

Thus, there is no reason from Goodey et al and Fisher et al. to eliminate the Goodey et al. gel permeation step. Additionally, Goodey et al. and Fisher et al. both teach against applicants' pH range of 5.0 - 6.0 in the negative mode cation exchange step. Further, as pointed out by the examiner in paragraph 19(D), neither Goodey et al nor Fisher et al. teach (1) repeating AE chromatography steps or (2) affinity chromatography run in the negative mode with respect to albumin and the positive mode with respect to glycoconjugates.. Although the Shaklai et al. reference may arguably supply these

missing steps, the references taken as a whole do not suggest to the skilled reader the combination and order of albumin purification steps first disclosed by applicants' specification and claims 83 and 87.

The nonglycosylated albumin from the affinity chromatography step in paragraph 7 on page 3812 of Shaklai et al. is glycosylated in the subsequent paragraph. Thus, Applicants submit that Shaklai et al. does not contemplate the use of such an affinity chromatography step in relation to other steps in applicants' processes of claims 83 and 87.

Moreover, Fisher et al. and Shaklai et al. were available well before the priority date of Goodey et al., yet Goodey et al. did not seek to incorporate their allegedly obvious steps. This is the epitome of unobviousness.

Accordingly, applicants respectfully solicit withdrawal for the subject rejection of claims 82 and 86 under 35 USC 103(a) for obviousness over Goodey et al. in view of Fisher et al. and Shaklai et al..

In paragraph 16 of the subject Office Action, the examiner rejects claims 58 and 94 under 35 USC 103(a) as being unpatentable over Goodey et al. (WO97/31947; cited in the IDS) in view of Fisher et al. (US 4,228,154; cited in IDS) as applied to claims 54 and 90 above, and further in view of Curling ("Methods of Plasma Protein Fractionation", pp. 77-91, 1980; cited in IDS).

Claims 58 and 94 are drawn to the methods of claim 54 and 90, respectively, wherein the initial albumin solution has an albumin concentration of 10-250 g/L. In paragraph 16(C), the examiner states that Curling teaches industrial scale purification of albumin on AE and CE columns, with 500g of albumin in 16 L (about 31 g/L albumin) loaded onto the column (Fig. 2, page 81, paragraphs 3-6; Table 1).

The examiner then states that it would have been prima facie obvious to one of ordinary skill in the art to have used initial albumin concentrations of Curling (greater than 10 g/L) in the combined method of Goodey et al. and Fisher et al. The motivation to do so, provided by Curling, would have been that purification of this albumin concentration resulted in a 97% pure product (page 82, second paragraph).

Applicants submit that the process of Curling does not provide motivation for using 10-250 g/L as the initial albumin concentration in applicants claimed process using negative mode CE for the following reasons:

(1) In the paragraph bridging the pages 80 and 81, Curling states: "After pH and ionic strength adjustment to pH 4.8, I = 0.07, the albumin fraction from DEAE-chromatography is applied to CM-Sepharose CL-6B equilibrated to the same conditions. In this step and under the above conditions albumin is bound." (emphasis added) Thus, Curling teaches a positive mode ion exchange chromatography and a pH of 4.8 - both according to Goodey et al. and contra to applicants' negative mode ion exchange chromatography and pH range of 5.0 - 6.0.

(2) The 97% purity factor is well below the minimum purity acceptable to Goodey et al. (99.0%). Thus, the skilled reader is not motivated to use such larger scale conditions to obtain even the minimum purity of Goodey et al., let alone the greater purity aimed for in applicants' claimed process.

(3) The paragraph referred to in Curling at the bottom of page 82 states: "The tandem ion exchange procedures give, by selective adsorption/desorption, an albumin product of approximately 97% purity, which although quite sufficient to meet Pharmacopoeia requirements shows some tendency towards product instability on storage or even immediately after obligatory heat treatment at 60°C. The amelioration of this product is described by Berglöf, this volume)." (emphasis added) Thus, the 97% purity comes with the caveat of instability.

Withdrawal of the rejection of claims 58 and 94 as being unpatentable over Goodey et al. in view of Fisher et al. as applied to claims 54 and 90 above, and further in view of Curling is therefore respectfully requested.

In paragraph 17 of the subject Office Action, the examiner rejects claims 68, 73, 103 and 108 under 35 USC 103(a) as being unpatentable over Goodey et al. (WO97/31947; cited in the IDS) in view of Fisher et al. (US 4,228,154; cited in IDS) as applied to claims 54, 67, 90 and 102 above, and further in view of Ohmura et al. (EP 0 570 916; cited in the IDS) and Chang (EP 0 422 769 A1; cited in the IDS).

Applicants respectfully request reconsideration and withdrawal of this rejection for the reasons presented below.

The subject claims 68 and 73 claim a pH range of 6.0 to 8.0 for the positive mode anion exchange of dependent claim 67. Claim 67 is dependent on independent claim 54. The subject claims 103 and 108 claim a pH range of 6.0 to 8.0 for the positive mode anion exchange of dependent claim 102. Claim 102 is dependent on independent claim 90. For the reasons enumerated in response to the examiner's rejection for obviousness in paragraph 14 of the Office Action, applicants maintain that independent claims 54 and 90 are patentable over Goodey et al. in view of Fisher et al. Neither Ohmura et al. nor Chang adds anything to the disclosure of Goodey et al. and Fisher et al. with respect to the examiner's rejection of claims 54 and 90 in paragraph 14 of the Office Action. In fact, Ohmura et al. supports the teaching of Goodey et al. to use positive mode cation exchange for the purification of albumin.

Accordingly, applicants submit that the subject dependent claims 68, 73, 102 and 108 are also patentable, and their allowance is respectfully solicited.

In paragraph 18 of the subject Office Action, the examiner rejects claims 68, 73, 103 and 108 under 35 USC 103(a) as being unpatentable over Goodey et al. (WO97/31947; cited in the IDS) in view of Fisher et al. (US 4,228,154; cited in IDS) as applied to claims 54, 67, 90 and 102 above, and further in view of Ohmura et al. (EP 0 570 916; cited in the IDS) and Chang (EP 0 422 769 A1; cited in the IDS).

Applicants respectfully request reconsideration and withdrawal of this rejection for the reasons presented below.

The subject claims 72 and 107 claim an elution buffer comprising 20-90mM phosphoric acid for the positive mode anion exchange of dependent claims 67 and 102, respectively (via intervening dependent claims 71 and 106, respectively). Claims 67 and 107 are, in turn, respectively dependent on independent claims 54 and 90.

As stated above regarding paragraph 17 of the Office Action, neither Ohmura et al. nor Chang adds anything to the disclosure of Goodey et al. and Fisher et al. with respect to

the examiner's rejection of claims 54 and 90 in paragraph 14 of the Office Action. In fact, as noted above, Ohmura et al. supports the teaching of Goodey et al. to use positive mode cation exchange for the purification of albumin

Thus, applicants submit that the subject dependent claims 72 and 107 are also patentable, and their allowance is respectfully solicited.

In paragraph 19 of the subject Office Action, the examiner rejects independent claims 83, 85, 87 and 89 under 35 USC 103(a) as being unpatentable over Goodey et al. (WO97/31947; cited in the IDS) in view of Fisher et al. (US 4,228,154; cited in IDS) and Shaklai et al. (J.Biol.Chem., vol.259, pp 3812-3817, 1984), and further in view Chang (EP 0 422 769 A1; cited in the IDS).

Applicants respectfully request reconsideration and withdrawal of the subject rejection for the reasons presented below.

Applicants submit that the combination of three references selected by the examiner to arrive at applicants' particular 13 step processes of independent claims 83 and 87 is not suggested in the references themselves. Accordingly, this combination is selected only in hindsight view of applicants' claims.

Goodey et al. discloses two specific 7 step processes as the second and third aspects of the invention disclosed therein. These are:

Goodey et al. page 2	Goodey et al. page 3 (& 38)
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6) positive AE	6) elution
7) elution	7) gel permeation
8) optional immobilized borate chrome	8) optional immobilized borate chrome

Goodey et al. does not mention the possibility of further purification steps and states on page 38 that that the purification process disclosed on page 3 (according to respective examples) is preferred. As seen above, both of these processes include a gel permeation step.

Fisher et al., on the other hand , discloses only three purification steps, namely, (1) contacting the cryosupernatant plasma or its equivalent with a finely divided lipoprotein abstract, (2) negative mode CE, and (3) negative mode AE. As pointed out by the examiner, Fisher et al.'s reason for using both CE and AE in the negative mode is to retain the albumin in solution throughout the process. In contrast, one of applicants' steps (ix) and (xi) is run in the positive mode.

Further, at the beginning of example 2, Fisher et al. states that the Cohn II + III supernatant albumin-containing material may be treated to remove alcohol and salt by gel filtration before step (1) above. Thus, it appears that Fisher et al. contemplates a gel permeation step as in both Goodey et al. 7 step processes. Applicants' processes of claims 83 and 87 do not include a gel permeation step.

As pointed out by the examiner, neither Goodey et al. nor Fisher et al. teach repeating AE chromatography steps. Additionally, as pointed out above (re paragraph 14), neither Goodey et al. nor Fisher et al. disclose running negative mode CE at a pH of 5.0 - 6.0. Goodey et al. states instead a preferred pH of 4.0 – 5.0 for CE at page 3, lines 18-21, and Fisher et al. teaches that cation exchange (CE) - in the negative mode - should be conducted at pH 4.5 - 4.9 (see column 2, lines 25-27). Thus, both Goodey et al. and Fisher et al. teach away from this condition for applicants' negative mode cation exchange chromatography step.

Thus, there is no reason from Goodey et al and Fisher et al. to eliminate the Goodey et al. gel permeation step. Additionally, Goodey et al. and Fisher et al. both teach against applicants' pH range of 5.0 - 6.0 in the negative mode cation exchange step. Further, as pointed out by the examiner in paragraph 19(D), neither Goodey et al nor Fisher et al. teach (1) repeating AE chromatography steps or (2) affinity chromatography run in the negative mode with respect to albumin and positive mode with respect to glycoconjugates. Although the Chang and Shaklai et al. references may arguably supply these missing steps, the references taken as a whole do not suggest to the

skilled reader the combination and order of steps first disclosed by applicants' specification and claims 83 and 87.

Further, the nonglycosylated albumin from the affinity chromatography step in paragraph 7 on page 3812 of Shaklai et al. is glycosylated in the subsequent paragraph. Thus, Applicants submit that Shaklai et al. does not contemplate the use of such an affinity chromatography step in relation to other steps in applicants' purification processes of claims 83 and 87.

Chang, on the cited page 4, lines 17-39, teaches using negative mode AE followed consecutively by positive mode AE. In applicants' claimed process, both CE and AE are used in steps (1) and (2) and are repeated after two affinity chromatography steps (in opposite modes). Such combination is not suggested by the references themselves, but only through hindsight use of applicants' disclosed and claimed process.

Moreover, Fisher et al., Shaklai et al. and Chang were all available well before the priority date of Goodey et al., yet Goodey et al. did not seek to incorporate their allegedly obvious steps. This is the epitome of unobviousness.

Accordingly, applicants respectfully solicit withdrawal for the subject rejection of claims 83, 85, 87 and 89 under 35 USC 103(a) as obviousness over Goodey et al. in view of Fisher et al. and Shaklai et al., and further in view Chang.

Allowance of the application as amended herein, including revised drawings, a Sequence Listing and a computer readable form of the Sequence Listing, is respectfully solicited. (The Statement and Notice To Comply with respect to the Sequence Listing and it computer readable form are also included with the response.)

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Should the Examiner have any questions regarding the above amendment and remarks, the Examiner is requested to contact the undersigned attorney.

Respectfully submitted,

Dated: 2/5/04

Arthur G. Seifert (Reg. No. 28,040)
Attorney for Applicant(s)

Aventis Behring L.L.C.
1020 First Avenue
King of Prussia, PA 19406
Telephone: 610-878-4772
Facsimile: 610-878-4334